STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 133433

To: Cybille Delacroix **Location:** rem/3a78/3c70 **Art Unit:** 1614 Friday, September 24, 2004 **Case Serial Number:** 10/624294	**From:** Beverly Shears **Location:** Remsen Bldg. RM 1A54 **Phone:** 571-272-2528 beverly.shears@uspto.gov

Search Notes

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: C Delacroix-M Examiner #: 71100 Date: 9-22-04
Art Unit: 1614 Phone Number 30 272-0572 Serial Number: 10/624,294
Mail Box and Bldg/Room Location: 43C70 43A78 Results Format Preferred (circle): PAPER DISK E-MAIL
If more than one search is submitted, please prioritize searches in order of need. MG'

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): PLEASE SEE ATTACHED

Earliest Priority Filing Date: _____

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search claim 1 + claim 13.

Key terms are highlighted.

Synonyms -> cancer, tumor, tumour, neoplasm neoplasias, carcinoma, sarcoma, adenocarcinoma melanoma.

Thanks

cm

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STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: Bowers C2528	NA Sequence (#)	STN ✓
Searcher Phone #:	AA Sequence (#)	Dialog
Searcher Location:	Structure (#)	Questel/Orbit
Date Searcher Picked Up:	Bibliographic	Dr.Link
Date Completed:	Litigation	Lexis/Nexis
Searcher Prep & Review Time:	Fulltext	Sequence Systems
Clerical Prep Time:	Patent Family	WWW/Internet
Online Time:	Other	Other (specify)

PTO-1590 (8-01)

Delacroix
10/624294


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     FILE 'REGISTRY' ENTERED AT 14:19:33 ON 24 SEP 2004
                E PHENSTATIN/CN 5
L1              1 S E3

     FILE 'CAPLUS' ENTERED AT 14:19:36 ON 24 SEP 2004
L1              1 SEA FILE=REGISTRY ABB=ON  PLU=ON  PHENSTATIN/CN
L2             13 SEA FILE=CAPLUS ABB=ON  PLU=ON  L1 OR PHENSTATIN
L3             11 SEA FILE=CAPLUS ABB=ON  PLU=ON  L2 AND (?NEOPLAS? OR ?CANCER?
                  OR ?CARCIN? OR ?TUMOUR? OR ?TUMOR? OR ?SARCOMA? OR ?MELANOMA?)

L3   ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2004 ACS on STN
ED   Entered STN:  01 Feb 2004
ACCESSION NUMBER:         2004:80535  CAPLUS
DOCUMENT NUMBER:          140:133864
TITLE:                    Localized delivery system for phenstatin
                          using N-isopropylacrylamide
INVENTOR(S):              Vernon, Brent; Powell, Steven
PATENT ASSIGNEE(S):       Arizona Board of Regents, Acting for and On Behalf of
                          Arizona State University, USA
SOURCE:                   PCT Int. Appl., 23 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    ---------------------    --------
     WO 2004009127         A1    20040129    WO 2003-US22833          20030721
         W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
            CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
            GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
            LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
            PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
            TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG,
            KZ, MD, RU, TJ
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
            CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
            NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
            GW, ML, MR, NE, SN, TD, TG
     US 2004052761         A1    20040318    US 2003-624294           20030721
PRIORITY APPLN. INFO.:                       US 2002-397182P      P   20020719
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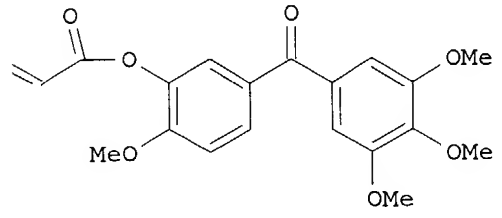


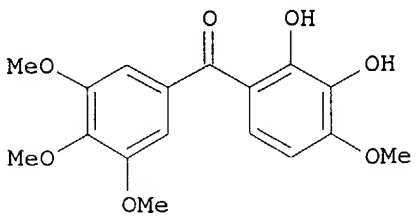
I

AB An injectable drug delivery system for localized release of **Phenstatin** to a **tumor** site over a period of time is provided. The drug delivery system comprises the thermoresponsive polymer N-isopropylacrylamide (NIPAAm) and **Phenstatin**, a toxic **antineoplastic** agent. The drug delivery system has a critical solution temperature (LCST) that causes it to change from the liquid state at room temperature when injected to a gel or semi-solid state after reaching the temperature of the human body in situ. Methods are given for delivering **Phenstatin** to a **cancerous tumor**. In these methods, the drug delivery system is injected into a tissue or into a **tumor** where it forms a gel. **Phenstatin** is slowly released from the polymer and exerts its cytotoxic, tubulin-related effects on the **tumor**. **Tumors** that may be treated by the present methods include, but are not limited to breast, prostate, lung and bowel **cancerous tumors**. I was prepared and polymerized with N-isopropylacrylamide to give a polymer drug delivery system.

IT **203448-32-2, Phenstatin**
RL: RCT (Reactant); RACT (Reactant or reagent)
(localized delivery system for **phenstatin** using N-isopropylacrylamide)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 13 Nov 2003
ACCESSION NUMBER: 2003:887467 CAPLUS
DOCUMENT NUMBER: 140:111179
TITLE: A Simple and Convenient Multigram Scale Synthesis of Hydroxyphenstatin: Potential **Cancer** Cell Growth Inhibitor
AUTHOR(S): Radha, Pedamallu
CORPORATE SOURCE: A.V. Rama Rao Research Foundation, Hyderabad, India
SOURCE: Synthetic Communications (2003), 33(22), 3869-3873
CODEN: SYNCAV; ISSN: 0039-7911
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:111179
GI



I

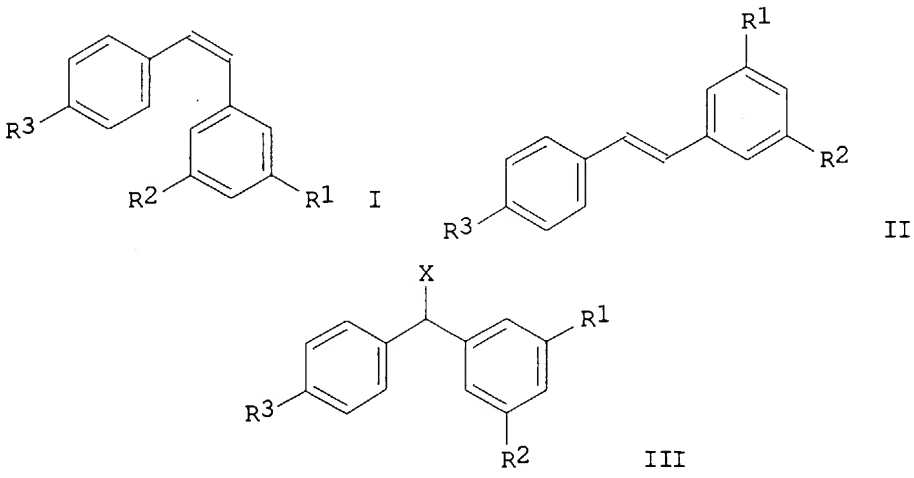
AB A simple and convenient two-step synthesis of hydroxyphenstatin (I) is reported by condensing 3,4,5-trimethoxybenzoic acid with pyrogallol and subsequent selective methylation with di-Me sulfate in presence of potassium carbonate.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 24 Oct 2003
ACCESSION NUMBER: 2003:836866 CAPLUS
DOCUMENT NUMBER: 139:337828
TITLE: Preparation of resveratrol and sodium resverastatin phosphate derivatives for use in pharmaceutical compositions as **antineoplastic** and antimicrobial agents
INVENTOR(S): Pettit, George R.; Grealish, Matthew P.
PATENT ASSIGNEE(S): Arizona Board of Regents, USA
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003086414	A1	20031023	WO 2003-US11008	20030410
W: CA, JP, US				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR				

PRIORITY APPLN. INFO.: US 2002-371782P P 20020410
OTHER SOURCE(S): CASREACT 139:337828
GI



AB Combretastatin A-4, resveratrol, resverastatin, benzophenone and benzhydrol derivs. and analogs, such as I, II and III [R1, R2, R3 = OH,

OMe; X = :O, OH], were prepared for therapeutic uses as **antineoplastic** and antimicrobial agents. Thus, (E)- and (Z)-3,5,4'-trimethoxystilbene were prepared in 91% overall yield via an olefination reaction of 4-methoxybenzyltriphenylphosphonium bromide and 3,5-dimethoxybenzaldehyde using BuLi in THF. The prepared compds. were assayed for inhibition of tubulin polymerization and colchicine binding and for activity against **cancer** cell lines, such as P388 leukemia and pancreas-a BXPC-3, and for activity against organisms, such as S. aureus, C. albicans and E. coli.

IT **203448-32-2P, Phenstatin**
RL: PAC (Pharmacological activity); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of resveratrol and sodium resverastatin phosphate derivs. for use in pharmaceutical compns. as **antineoplastic** and antimicrobial agents)

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 04 Mar 2003
ACCESSION NUMBER: 2003:162635 CAPLUS
DOCUMENT NUMBER: 140:35300
TITLE: Structure-activity and crystallographic analysis of benzophenone derivatives-the potential **anticancer** agents. [Erratum to document cited in CA139:46374]
AUTHOR(S): Hsieh, Hsing-Pang; Liou, Jing-Ping; Lin, Ying-Ting; Mahindroo, Neeraj; Chang, Jang-Yang; Yang, Yung-Ning; Chern, Shuenn-Shing; Tan, Uan-Kang; Chang, Chun-Wei; Chen, Tung-Wei; Lin, Chi-Hung; Chang, Ying-Ying; Wang, Chiung-Chiu
CORPORATE SOURCE: Divison of Biotechnology and Pharmaceutical Research, National Health Research Institutes, Taipei, 114, Taiwan
SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(5), 977
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The incorrect citation details (Volume/Yr) were given at the top of each page of the article. The correct bibliog. details are: Bioorg. & Medicinal Chemical Letters 13 (2003) 101-105.

IT **203448-32-2, Phenstatin**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-activity and crystallog. anal. of benzophenone derivs. as potential **antitumor** agents (Erratum))

L3 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 06 Dec 2002
ACCESSION NUMBER: 2002:925011 CAPLUS
DOCUMENT NUMBER: 139:46374

TITLE: Structure-activity and crystallographic analysis of benzophenone derivatives-the potential **anticancer** agents

AUTHOR(S): Hsieh, Hsing-Pang; Liou, Jing-Ping; Lin, Ying-Ting; Mahindroo, Neeraj; Chang, Jang-Yang; Yang, Yung-Ning; Chern, Shuenn-Shing; Tan, Uan-Kang; Chang, Chun-Wei; Chen, Tung-Wei; Lin, Chi-Hung; Chang, Ying-Ying; Wang, Chiung-Chiu

CORPORATE SOURCE: Sec. 6, Division of Biotechnology and Pharmaceutical Research, National Health Research Institutes, Taipei, Taiwan, 114, Peop. Rep. China

SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(1), 101-105
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 139:46374

AB Compds. 1-5, structurally related to combretastatin A-4 showed excellent cytotoxic activities against a panel of human **cancer** cell lines including multi-drug resistant cell lines. The x-ray three-dimensional structural anal. shows that proton donor in B ring may be required for cytotoxic activity, with intermol. hydrogen bonding playing an important role.

IT **203448-32-2, Phenstatin**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-activity and crystallog. anal. of benzophenone derivs. as potential **antitumor** agents)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN

ED Entered STN: 10 May 2002

ACCESSION NUMBER: 2002:348358 CAPLUS

DOCUMENT NUMBER: 137:87838

TITLE: **Antineoplastic** Agents. 465. Structural Modification of Resveratrol: Sodium Resverastatin Phosphate

AUTHOR(S): Pettit, George R.; Grealish, Matthew P.; Jung, M. Katherine; Hamel, Ernest; Pettit, Robin K.; Chapuis, J. Charles; Schmidt, Jean M.

CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, AZ, 85287-2404, USA

SOURCE: Journal of Medicinal Chemistry (2002), 45(12), 2534-2542
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 137:87838

AB As an extension of structure/activity investigations of resveratrol, **phenstatin**, and the **cancer** antiangiogenesis drug sodium combretastatin A-4 phosphate, syntheses of certain related stilbenes and benzophenones were undertaken. The tri-Me ether derivative of (Z)-resveratrol

exhibited the strongest activity (GI50 = 0.01-0.001 μg/mL) against a minipanel of human **cancer** cell lines. A monodemethylated derivative was converted to prodrug (sodium resverastatin phosphate) for further biol. evaluation. The antitubulin and antimicrobial activities of selected compds. were also evaluated.

IT **203448-32-2, Phenstatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation and **antitumor** structure activity relationships of resveratrol analogs)

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 24 Aug 2001
ACCESSION NUMBER: 2001:617806 CAPLUS
DOCUMENT NUMBER: 135:175360
TITLE: Antiangiogenic combinations of nitroacridine derivs. and inhibition of **tumor** growth and metastasis and compositions thereof
INVENTOR(S): Raj, Tiwari; Miller, Daniel; Konopa, Jerzy Kazimierz; Wysocka-Skrzela, Barbara
PATENT ASSIGNEE(S): New York Medical College, USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001060351	A2	20010823	WO 2001-US5276	20010216
WO 2001060351	A3	20020124		
W: AL, AU, BA, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002037831	A1	20020328	US 2001-789496	20010216
EP 1261325	A2	20021204	EP 2001-910944	20010216
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-183529P P 20000218
WO 2001-US5276 W 20010216

AB The invention is directed to 1-nitroacridine derivs. as antiangiogenic substances and use in **tumor** growth and metastasis. Inhibitor(s) compns. as well as methods for using said compns. for inhibiting or preventing **tumor** growth, particularly, prostate **cancer** cells growth and metastases are presented.

IT **203448-32-2, Phenstatin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antiangiogenic combinations of nitroacridine derivs. and inhibition of **tumor** growth and metastasis)

L3 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 25 Aug 2000
ACCESSION NUMBER: 2000:592560 CAPLUS
DOCUMENT NUMBER: 133:198575
TITLE: Compositions and methods for use in targeting vascular destruction
INVENTOR(S): Pero, Ronald W.; Sherris, David
PATENT ASSIGNEE(S): Oxigene, Inc., USA
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048606	A1	20000824	WO 2000-US3996	20000216
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2358925	AA	20000824	CA 2000-2358925	20000216
EP 1152764	A1	20011114	EP 2000-914606	20000216
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JP 2002537262	T2	20021105	JP 2000-599398	20000216
US 6538038	B1	20030325	US 2000-505402	20000216
US 2003109500	A1	20030612	US 2002-218833	20020814
PRIORITY APPLN. INFO.:			US 1999-120478P	P 19990218
			US 2000-505402	A1 20000216
			WO 2000-US3996	W 20000216

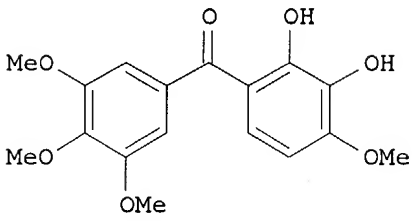
OTHER SOURCE(S): MARPAT 133:198575

AB Treatment of warm-blooded animals having a **tumor** or non-malignant hypervascularization, by administering a sufficient amount of a cytotoxic agent formulated into a phosphate prodrug form having substrate specificity for microvessel phosphatases, so that microvessels are destroyed preferentially over other normal tissues, because the less cytotoxic prodrug form is converted to the highly cytotoxic dephosphorylated form.

IT **203448-32-2D, Phenstatin,** derivs.
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(prodrugs for use in targeting vascular destruction)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 27 Jun 2000
ACCESSION NUMBER: 2000:425859 CAPLUS
DOCUMENT NUMBER: 133:207717
TITLE: **Antineoplastic** Agents. 443. Synthesis of the **Cancer** Cell Growth Inhibitor Hydroxyphenstatin and Its Sodium Diphosphate Prodrug
AUTHOR(S): Pettit, George R.; Grealish, Matthew P.; Herald, Delbert L.; Boyd, Michael R.; Hamel, Ernest; Pettit, Robin K.
CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, AZ, 85287-2404, USA
SOURCE: Journal of Medicinal Chemistry (2000), 43(14), 2731-2737
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

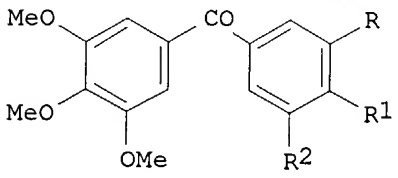
AB A structure-activity relationship (SAR) study of the South African willow tree (Combretum caffrum) **antineoplastic** constituent combretastatin A-4 led to the discovery of a potent **cancer** cell growth inhibitor designated **phenstatin**. This benzophenone derivative of combretastatin A-4 showed remarkable **antineoplastic** activity, and the benzophenone derivative of combretastatin A-1 was therefore synthesized. The benzophenone, designated hydroxyphenstatin (I), was synthesized by coupling of a protected bromobenzene and a benzaldehyde to give the benzhydrol with subsequent oxidation to the ketone. Hydroxyphenstatin was converted to the sodium phosphate prodrug by a dibenzyl phosphite phosphorylation and subsequent benzyl cleavage. While hydroxyphenstatin I was a potent inhibitor of tubulin polymerization with activity comparable to that of combretastatin A-1, the phosphorylated derivative of I was inactive.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 23 Jul 1999
ACCESSION NUMBER: 1999:451177 CAPLUS
DOCUMENT NUMBER: 131:73506
TITLE: Synthesis and formulation of **phenstatin** and

related prodrugs for use as **antitumor** agents
INVENTOR(S): Pettit, George R.; Toki, Brian
PATENT ASSIGNEE(S): Arizona State University, USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9934788	A1	19990715	WO 1999-US475	19990109
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2314510	AA	19990715	CA 1999-2314510	19990109
EP 1045689	A1	20001025	EP 1999-902133	19990109
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002500184	T2	20020108	JP 2000-527239	19990109
PRIORITY APPLN. INFO.:			US 1998-70878P P	19980109
			WO 1999-US475 W	19990109

OTHER SOURCE(S): MARPAT 131:73506
GI



I

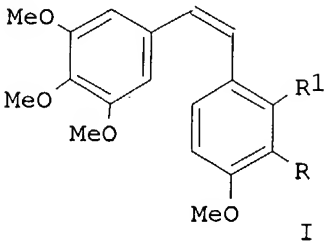
AB **Phenstatin** I (R = H, R1 = OMe, R2 = OH) and related prodrugs I [R = H, OMe, Me, Cl, F; R1 = H, OMe; R2 = OPO3Na2, OPO3H2, OAc, OMe, Me, Cl, F; R1R2 = OCH2O] were prepared and formulated for use as **antineoplastic** agents. Thus, **phenstatin** was converted to the sodium phosphate prodrug I (R = H, R1 = OMe, R2 = OPO3Na2) by a dibenzylphosphite phosphorylation and subsequent hydrogenolysis sequence. **Phenstatin** was found to be a potent inhibitor of tubulin polymerization and the binding of colchicine to tubulin comparable to combretastatin A-4.

IT **203448-32-2P, Phenstatin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(synthesis and formulation of **phenstatin** and related prodrugs for use as **antitumor** agents)

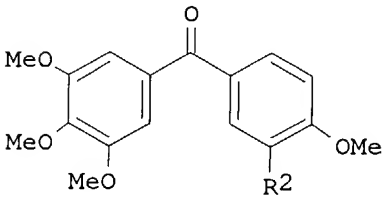
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 05 May 1998
ACCESSION NUMBER: 1998:253141 CAPLUS

DOCUMENT NUMBER: 128:230173
TITLE: **Antineoplastic** Agents. 379. Synthesis of **Phenstatin** Phosphate
AUTHOR(S): Pettit, George R.; Toki, Brian; Herald, Delbert L.; Verdier-Pinard, Pascal; Boyd, Michael R.; Hamel, Ernest; Pettit, Robin K.
CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-1604, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(10), 1688-1695
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



II

AB A structure-activity relationship (SAR) study of the South African willow tree (Combretum caffrum) **antineoplastic** constituent combretastatin A-4 (I; R = OH, R1 = H) directed at maintaining the (Z)-stilbene relationship of the olefin di-Ph substituents led to synthesis of a potent **cancer** cell growth inhibitor designated **phenstatin** (II; R2 = OH). Initially **phenstatin** silyl ether (II; R2 = OSiMe2CMe3) was unexpectedly obtained by Jacobsen oxidation of combretastatin A-4 silyl ether (I; R = OSiMe2CMe2, R1 = H), and the parent **phenstatin** (II; R2 = OH) was later synthesized in quantity. **Phenstatin** was converted to the sodium phosphate prodrug [II; R2 = OP(O)(ONa)2] by a dibenzyl phosphite phosphorylation and subsequent hydrogenolysis sequence. **Phenstatin** (II; R2 = OH) inhibited growth of the pathogenic bacterium Neisseria gonorrhoeae and was a potent inhibitor of tubulin polymerization and the binding of colchicine to tubulin comparable to combretastatin A-4 (I; R = OH, R1 = H). Interestingly, the prodrugs were found to have reduced activity in these biochem. assays. While no significant tubulin activity was observed with the phosphorylated derivative of combretastatin A-4 (I; R = OH, R1 = H), phosphate II [R2 = OP(O)(ONa)2] retained detectable inhibitory effects in both assays.

IT **203448-32-2P, Phenstatin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant

or reagent)
(structure-activity relationship of the **antineoplastic** agent combretastatin A-4)
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 14:21:35 ON 24 SEP 2004)
L4 27 S L3

L1 1 SEA FILE=REGISTRY ABB=ON PLU=ON PHENSTATIN/CN
L2 13 SEA FILE=CAPLUS ABB=ON PLU=ON L1 OR PHENSTATIN
L5 24 SEA L2 AND (ANTINEOPLAS? OR ANTICANCER? OR ANTICARCIN? OR ANTITUMOUR? OR ANTITUMOR? OR ANTISARCOMA? OR ANTIMELANOMA?)

L6 27 L4 OR L5

PROCESSING COMPLETED FOR L6
L7 14 DUP REM L6 (13 DUPLICATES REMOVED)

L7 ANSWER 1 OF 14 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-180271 [17] WPIDS
DOC. NO. CPI: C2004-071233
TITLE: Drug delivery system for localized delivery of **phenstatin** to treat **tumor** tissue e.g. breast tissue comprises polymer poly(N-isopropylacrylamide) chemically bound to **phenstatin.**
DERWENT CLASS: A14 A96 B05
INVENTOR(S): POWELL, S; VERNON, B
PATENT ASSIGNEE(S): (POWE-I) POWELL S; (UYAR-N) UNIV ARIZONA STATE; (VERN-I) VERNON B
COUNTRY COUNT: 105
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004009127	A1	20040129	(200417)*	EN	23
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW					
US 2004052761	A1	20040318	(200421)		
AU 2003254092	A1	20040209	(200450)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004009127	A1	WO 2003-US22833	20030721
US 2004052761	A1 Provisional	US 2002-397182P	20020719
		US 2003-624294	20030721
AU 2003254092	A1	AU 2003-254092	20030721

Searcher : Shears 571-272-2528

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003254092	A1 Based on	WO 2004009127

PRIORITY APPLN. INFO: US 2002-397182P 20020719; US 2003-624294 20030721

AN 2004-180271 [17] WPIDS

AB WO2004009127 A UPAB: 20040310

NOVELTY - A drug delivery system comprises polymer poly(N-isopropylacrylamide) chemically bound to **phenstatin**.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for the preparation of the drug delivery system, comprising:

(a) preparing **phenstatin** acrylate; and

(b) polymerizing the **phenstatin** acrylate and poly(N-isopropylacrylamide).

ACTIVITY - Cytostatic.

No biological data is given.

MECHANISM OF ACTION - Tubulin polymerization inhibitor; Inhibitor of colchicines binding to tubulin.

USE - For the treatment of **cancerous tumor** tissue e.g. breast, prostate, lung and bowel tissue (claimed).

ADVANTAGE - Localized delivery of the **phenstatin** reduces the systemic levels of **phenstatin**, thus minimizing undesirable side effects. The N-isopropylacrylamide has a lower critical solution temperature above 25 deg. C and below body temperature with quick phase transition so that **phenstatin** is slowly released from the polymer and exerts its cytotoxic, tubulin-related effects on the **tumor**.

Dwg.0/2

L7 ANSWER 2 OF 14 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:312105 BIOSIS

DOCUMENT NUMBER: PREV200400313623

TITLE: Synthesis and structure-activity relationships of 3-aminobenzophenones as antimitotic agents.

AUTHOR(S): Liou, Jing-Ping; Chang, Jang-Yang; Chang, Chun-Wei; Chang, Chi-Yen; Mahindroo, Neeraj; Kuo, Fu-Ming; Hsieh, Hsing-Pang [Reprint Author]

CORPORATE SOURCE: Div Biotechnol and Pharmaceut ResMed Synth Lab, Natl Hlth Res Inst, 9F,161,Sec 6,Min Chiuan E Rd, Taipei, 114, Taiwan hphsieh@nhri.org.tw

SOURCE: Journal of Medicinal Chemistry, (May 20 2004) Vol. 47, No. 11, pp. 2897-2905. print.
ISSN: 0022-2623 (ISSN print).

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 15 Jul 2004
Last Updated on STN: 15 Jul 2004

AB A new series of 3-aminobenzophenone compounds as potent inhibitors of tubulin polymerization was discovered based on the mimic of the aminocombretastatin molecular skeleton. Lead compounds 5 and 11, with alkoxy groups at the C-4 position of B-ring, were potent cytotoxic agents

and inhibitors of tubulin polymerization through the binding to the colchicine-binding site of tubulin. The corresponding antitubulin activities of 5 and 11 were similar to or greater than combretastatin A-4 and AVE-8063. Replacement of the methoxy group with a chloro group in the B ring of aminobenzopheneones (3, 8, and 9) caused drastic decrease in cytotoxic and antitubulin activity except in compounds 4 and 10, which could result from a unique alignment between chloro and amino groups located at the para position to each other. SAR information revealed that introduction of an amino group at the C-3 position in B ring of benzophenones, in addition to a methoxy group at the C-4 position, plays an important role for maximal cytotoxicity.

L7 ANSWER 3 OF 14 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-210121 [20] WPIDS
DOC. NO. CPI: C2003-053505
TITLE: **Antitumor** agents comprise a tublin-polymerization inhibitor and antiinflammatory agent for simultaneous or separate administration, useful in the treatment, improvement, inhibition of progress and prevention of **tumors**.
DERWENT CLASS: B04
INVENTOR(S): MORINAGA, Y; NIHEI, Y; SUGA, Y; SUZUKI, M
PATENT ASSIGNEE(S): (AJIN) AJINOMOTO CO INC
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003000290	A1	20030103	(200320)*	JA	32
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
EP 1407784	A1	20040414	(200426)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
AU 2002313260	A1	20030108	(200460)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003000290	A1	WO 2002-JP6260	20020624
EP 1407784	A1	EP 2002-738789	20020624
		WO 2002-JP6260	20020624
AU 2002313260	A1	AU 2002-313260	20020624

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1407784	A1 Based on	WO 2003000290
AU 2002313260	A1 Based on	WO 2003000290

PRIORITY APPLN. INFO: JP 2001-191067 20010625
AN 2003-210121 [20] WPIDS
AB WO2003000290 A UPAB: 20030324
NOVELTY - New **antitumor** agents (A) comprise:
(1) a tublin-polymerization inhibitor (I) having **antitumor** activity; and
(2) an antiinflammatory agent (II), optionally in combined use.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of treating **tumors** comprising administering (A) into the body.
ACTIVITY - Cytostatic; Antiinflammatory; Immunosuppressive.
The separate administration of (Z)-N-(2-methoxy-5-(2-(3,4,5-trimethoxyphenyl)vinyl)phenyl)-L-serinamide hydrochloride and dexamethasone to malignant **tumor**-transplanted rats was performed and the **antitumor** effects was studied and ascertained.
No further information given.
MECHANISM OF ACTION - Tublin-Polymerization Inhibitor.
USE - (A) are used to provide **antitumor** agents with reduced toxicity. (I) and (II) are used in drugs on their own, or in combination by separate or simultaneous administration (all claimed). (A) are used in the treatment, improvement, inhibition of progress and prevention of **tumors**.
ADVANTAGE - In these preparations, toxicity of the tublin-polymerization inhibitor (I) is greatly reduced while maintaining its therapeutic efficacy, whilst increasing its fatal dose limit to broaden the safety range.
Dwg.0/2

L7 ANSWER 4 OF 14 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:1062658 SCISEARCH
THE GENUINE ARTICLE: 747DK
TITLE: A simple and convenient mnltigram scale synthesis of hydroxyphenstatin: Potential **cancer** cell growth inhibitor
AUTHOR: Radha P (Reprint)
CORPORATE SOURCE: Av Rama Rao Res Fdn, Hyderabad 500007, Andhra Pradesh, India (Reprint)
COUNTRY OF AUTHOR: India
SOURCE: SYNTHETIC COMMUNICATIONS, (14 NOV 2003) Vol. 33, No. 22, pp. 3869-3873.
Publisher: MARCEL DEKKER INC, 270 MADISON AVE, NEW YORK, NY 10016 USA.
ISSN: 0039-7911.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 6
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB A simple and convenient two-step synthesis of hydroxyphenstatin (2) is reported by condensing 3,4,5-trimethoxybenzoic acid with pyrogallol and subsequent selective methylation with dimethyl sulphate in presence of potassium carbonate.

L7 ANSWER 5 OF 14 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 1

ACCESSION NUMBER: 2003:522888 BIOSIS
DOCUMENT NUMBER: PREV200300518687
TITLE: N-isopropylacrylamide copolymer with isovanillin (Model of chemotherapy agent **phenstatin**).
AUTHOR(S): Powell, S. [Reprint Author]; Williams, M. D.; Nieman, R. A.; Vernon, B. [Reprint Author]
CORPORATE SOURCE: Department of Bioengineering, Arizona State University, Tempe, AZ, 85287-9709, USA
SOURCE: Journal of Controlled Release, (28 August 2003) Vol. 91, No. 1-2, pp. 256-258. print.
Meeting Info.: Proceedings of the 2nd International Symposium on Tumor Targeted Delivery Systems. Bethesda, MD, USA. September 23-25, 2002. National Cancer Institute; Controlled Release Society.
ISSN: 0168-3659 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Nov 2003
Last Updated on STN: 5 Nov 2003

L7 ANSWER 6 OF 14 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002450179 EMBASE
TITLE: Structure-activity and crystallographic analysis of benzophenone derivatives - The potential **anticancer** agents.
AUTHOR: Hsieh H.-P.; Liou J.-P.; Lin Y.-T.; Mahindroo N.; Chang J.-Y.; Yang Y.-N.; Chern S.-S.; Tan U.-K.; Chang C.-W.; Chen T.-W.; Lin C.-H.; Chang Y.-Y.; Wang C.-C.
CORPORATE SOURCE: H.-P. Hsieh, Div. of Biotechnol./Pharmaceut. Res., National Health Research Institutes, Min-Chiuan East Road, Taipei 114, Taiwan,Province of China. hphsieh@nhri.org.tw
SOURCE: Bioorganic and Medicinal Chemistry Letters, (6 Jan 2003) 13/1 (101-105).
Refs: 29
ISSN: 0960-894X CODEN: BMCLE8
PUBLISHER IDENT.: S 0960-894X(02)00850-8
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Compounds 1-5, structurally related to combretastatin A-4 showed excellent cytotoxic activities against a panel of human **cancer** cell lines including multi-drug resistant cell lines. The X-ray three-dimensional structural analysis shows that proton donor in B ring may be required for cytotoxic activity, with intermolecular hydrogen bonding playing an important role. .COPYRGT. 2002 Elsevier Science Ltd. All rights reserved.

L7 ANSWER 7 OF 14 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002198528 EMBASE

TITLE: Synthesis and structure-activity relationship of 2-aminobenzophenone derivatives as antimitotic agents.
AUTHOR: Liou J.-P.; Chang C.-W.; Song J.-S.; Yang Y.-N.; Yeh C.-F.; Tseng H.-Y.; Lo Y.-K.; Chang Y.-L.; Chang C.-M.; Hsieh H.-P.
CORPORATE SOURCE: H.-P. Hsieh, Division of Biotechnology, National Health Research Institutes, 128 Yen-Chiu-Yuan Road, Sec II, Taipei 115, Taiwan,Province of China. hphsieh@nhri.org.tw
SOURCE: Journal of Medicinal Chemistry, (6 Jun 2002) 45/12 (2556-2562).
Refs: 33
ISSN: 0022-2623 CODEN: JMCMAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A new type of inhibitor of tubulin polymerization was discovered on the basis of the combretastatin molecular skeleton. The lead compounds in this series, compounds 6 and 7, strongly inhibited tubulin polymerization in vitro and significantly arrested cells at the G(2)/M phase. Compounds 6 and 7 yielded 50- to 100-fold lower IC(50) values than did combretastatin A-4 against Colo 205, NUGC3, and HA22T human **cancer** cell lines as well as similar or greater growth inhibitory activities than did combretastain A-4 against DLD-1, HR, MCF-7, DU145, HONE-1, and MES-SA/DX5 human **cancer** cell lines. Structure-activity relationship information revealed that introduction of an amino group at the ortho position of the benzophenone ring plays an integral role for increased growth inhibition.

L7 ANSWER 8 OF 14 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002309212 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12036362
TITLE: **Antineoplastic** agents. 465. Structural modification of resveratrol: sodium resverastatin phosphate.
AUTHOR: Pettit George R; Grealish Matthew P; Jung M Katherine; Hamel Ernest; Pettit Robin K; Chapuis J-Charles; Schmidt Jean M
CORPORATE SOURCE: Department of Chemistry and Biochemistry, Cancer Research Institute, Arizona State University, P.O. Box 872404, Tempe, AZ 85287-2404, USA.. bpettit@asu.edu
CONTRACT NUMBER: CA 44344-05-12 (NCI)
N01-CO-56000 (NCI)
R01 CA 90441-01 (NCI)
SOURCE: Journal of medicinal chemistry, (2002 Jun 6) 45 (12) 2534-42.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020611

Searcher : Shears 571-272-2528

Last Updated on STN: 20020628
Entered Medline: 20020627

AB As an extension of structure/activity investigations of resveratrol (1), **phenstatin** (2c), and the **cancer** antiangiogenesis drug sodium combretastatin A-4 phosphate (2b), syntheses of certain related stilbenes (14) and benzophenones (16) were undertaken. The trimethyl ether derivative of (Z)-resveratrol (4a) exhibited the strongest activity (GI(50) = 0.01-0.001 microg/mL) against a minipanel of human **cancer** cell lines. A monodemethylated derivative (14c) was converted to prodrug 14n (sodium resverastatin phosphate) for further biological evaluation. The antitubulin and antimicrobial activities of selected compounds were also evaluated.

L7 ANSWER 9 OF 14 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2002:947624 SCISEARCH
THE GENUINE ARTICLE: 615ZW
TITLE: Discovery and development of antimitotic agents that inhibit tubulin polymerisation for the treatment of **cancer**
AUTHOR: Li Q (Reprint); Sham H L
CORPORATE SOURCE: Abbott Labs, Canc Res, R47S, AP-10, 100 Abbott Pk Rd, Abbott Pk, IL 60064 USA (Reprint); Abbott Labs, Canc Res, Abbott Pk, IL 60064 USA
COUNTRY OF AUTHOR: USA
SOURCE: EXPERT OPINION ON THERAPEUTIC PATENTS, (NOV 2002) Vol. 12, No. 11, pp. 1663-1702.
Publisher: ASHLEY PUBLICATIONS LTD, UNITEC HOUSE, 3RD FL, 2 ALBERT PLACE, FINCHLEY CENTRAL, LONDON N3 1QB, ENGLAND.
ISSN: 1354-3776.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 370

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Antimitotic agents have generated considerable interest among cytotoxic agents due to the tremendous success of the taxanes and the widespread use of the Vinca alkaloids in clinical oncology. Renewed interest in tubulin polymerisation inhibitors has been generated by the hope that non-multi-drug resistance (MDR) substrates that interact with tubulin at sites near to, overlapping with or different from those of the taxanes or Vinca alkaloids can be discovered. In this article, new antimitotic agents that inhibit tubulin polymerisation for the treatment of **cancer** are reviewed, with greater emphasis being focused on the small molecule colchicine site binders. Compounds that induce metaphase arrest, by other novel mechanisms, are summarised. Results of clinical trials of drug candidates that fall into these classes are also briefly discussed. The patent literature was surveyed from January 1998 through May 2002.

L7 ANSWER 10 OF 14 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2002:506413 SCISEARCH
THE GENUINE ARTICLE: 561VL
TITLE: Small-molecule, tubulin-binding compounds as vascular targeting agents
AUTHOR: Marx M A (Reprint)
CORPORATE SOURCE: Pfizer Corp, Pfizer Global Res & Dev, MS 8118W-352 Eastern

Point Rd, Groton, CT 06340 USA (Reprint); Pfizer Corp, Pfizer Global Res & Dev, Groton, CT 06340 USA
COUNTRY OF AUTHOR: USA
SOURCE: EXPERT OPINION ON THERAPEUTIC PATENTS, (JUN 2002) Vol. 12, No. 6, pp. 769-776.
Publisher: ASHLEY PUBLICATIONS LTD, UNITEC HOUSE, 3RD FL, 2 ALBERT PLACE, FINCHLEY CENTRAL, LONDON N3 1QB, ENGLAND.
ISSN: 1354-3776.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 74

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Vascular targeting or vascular damaging agents are directed toward established blood vessels, making them different from antiangiogenic agents, which inhibit one or more of the processes of neo-vascularisation. This emerging area of **cancer** drug discovery is currently being clinically tested and there is growing activity directed toward the identification of new antivascular agents. This review summarises key aspects of recent patents and patent applications referring to **cancer** chemotherapy and **cancer** drug discovery that involve the targeting or destruction of established vasculature. This review focuses on applications that have been published between January 2000 and December 2001, with earlier, selected references included. Small molecule approaches, such as analogues of combretastatin A-4 (CA4) and colchicine, as well as other novel chemotypes, are the major focus of this review.

L7 ANSWER 11 OF 14 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-558251 [51] WPIDS
DOC. NO. CPI: C2000-166230
TITLE: Treating vascular proliferative disorders, e.g. **cancer** or psoriasis, by administration of non-cytotoxic prodrug other than combretastatin A4.
DERWENT CLASS: B05
INVENTOR(S): LIPPERT, J W; PETTIT, G R; PERO, R W; SHERRIS, D; CHEN, Z; MOCHARLA, V P; PINNEY, K G
PATENT ASSIGNEE(S): (OXIG-N) OXI-GENE INC; (UYAR-N) UNIV ARIZONA; (OXIG-N) OXIGENE INC; (UYBA-N) UNIV BAYLOR; (CHEN-I) CHEN Z; (MOCH-I) MOCHARLA V P; (PERO-I) PERO R W; (PINN-I) PINNEY K G; (SHER-I) SHERRIS D
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000048606	A1	20000824	(200051)*	EN	34
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
AU 2000035973	A	20000904	(200103)		
EP 1152764	A1	20011114	(200175)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					

JP 2002537262	W	20021105 (200304)	42	
US 6538038	B1	20030325 (200325)		
US 2003109500	A1	20030612 (200340)		
MX 2001008291	A1	20020101 (200362)		
CA 2455956	A1	20000824 (200425)	EN	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000048606	A1	WO 2000-US3996	20000216
AU 2000035973	A	AU 2000-35973	20000216
EP 1152764	A1	EP 2000-914606	20000216
		WO 2000-US3996	20000216
JP 2002537262	W	JP 2000-599398	20000216
		WO 2000-US3996	20000216
US 6538038	B1 Provisional	US 1999-120478P	19990218
		US 2000-505402	20000216
US 2003109500	A1 Provisional	US 1999-120478P	19990218
	Cont of	US 2000-505402	20000216
		US 2002-218833	20020814
MX 2001008291	A1	WO 2000-US3996	20000216
		MX 2001-8291	20010816
CA 2455956	A1 Div ex	CA 2000-2358925	20000216
		CA 2000-2455956	20000216

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000035973	A Based on	WO 2000048606
EP 1152764	A1 Based on	WO 2000048606
JP 2002537262	W Based on	WO 2000048606
US 2003109500	A1 Cont of	US 6538038
MX 2001008291	A1 Based on	WO 2000048606

PRIORITY APPLN. INFO: US 1999-120478P 19990218; US 2000-505402 20000216; US 2002-218833 20020814

AN 2000-558251 [51] WPIDS

AB WO 200048606 A UPAB: 20040514

NOVELTY - Treating hypervascularization by administration of phosphate prodrug of e.g. tubulin binder, other than combretastatin A4 is new.

DETAILED DESCRIPTION - Treating a vascular proliferative disorder comprises administration of an amount of a prodrug other than combretastatin A4 disodium phosphate effective to achieve targeted vascular destruction of a locality of proliferating vasculature. The prodrug is non-cytotoxic but is convertible to a cytotoxic drug by action of an endothelial enzyme selectively induced at enhanced levels at sites of vascular proliferation.

An INDEPENDENT CLAIM is included for a identifying prodrugs suitable for use in the above method comprising:

(a) culturing proliferating endothelial cells and other cells which are non-malignant, in the presence of a prodrug other than combretastatin A4 disodium phosphate for a limited time period;

(b) comparing the respective cultures to determine whether the

culture of proliferating endothelial cells exhibits a greater cytotoxic effect than the culture of other cells; and

(c) if so, culturing the other cells in the presence of the prodrug and an endothelial enzyme selectively induced at enhanced levels at sites of vascular proliferation, enhanced cytotoxic effect with respect to the other cells in the presence of the enzyme as compared to the cytotoxic effects in the initial culture of the other cells indicating suitability of the prodrug for such methods.

ACTIVITY - Cytostatic; antipsoriatic; antiinflammatory.

MECHANISM OF ACTION - Tubulin-Binder. Combretastatin A1 in cytotoxic form via non-cytotoxic combretastatin A nicotinamide PO4 prodrug exhibited IC50 values of 10-15 micro M and 10 micro M against human microvesel endothelial cells and human diploid fibroblasts respectively.

USE - The methods are useful for targeting the microvessel destruction model for the treatment of **cancer**, Karposi's **sarcoma** and other, non-malignant vascular proliferative disorders such as macular degeneration, psoriasis and restenosis and inflammatory diseases characterized by vascular proliferation.

ADVANTAGE - Microvessels are destroyed preferentially over other normal tissues because the less cytotoxic prodrug form is converted to the highly cytotoxic de-phosphorylated form. Tubulin binding agents are preferred because they can be transformed from water insolubility to water solubility, tubulin binding agents to non-tubulin binding agents and cytotoxicity to non-cytotoxicity by phosphate prodrug formulation. Dwg.0/5

L7 ANSWER 12 OF 14 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2000353487 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10893310
TITLE: **Antineoplastic** agents. 443. Synthesis of the **cancer** cell growth inhibitor hydroxyphenstatin and its sodium diphosphate prodrug.
AUTHOR: Pettit G R; Grealish M P; Herald D L; Boyd M R; Hamel E; Pettit R K
CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, P.O. Box 872404, Tempe, Arizona 85287-2404, USA.
SOURCE: Journal of medicinal chemistry, (2000 Jul 13) 43 (14) 2731-7.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000803

AB A structure-activity relationship (SAR) study of the South African willow tree (Combretum caffrum) **antineoplastic** constituent combretastatin A-4 (3b) led to the discovery of a potent **cancer** cell growth inhibitor designated **phenstatin** (5a). This benzophenone derivative of combretastatin A-4 showed remarkable **antineoplastic** activity, and the benzophenone derivative of combretastatin A-1 was therefore synthesized. The benzophenone, designated hydroxyphenstatin (6a), was synthesized by coupling of a

protected bromobenzene and a benzaldehyde to give the benzhydrol with subsequent oxidation to the ketone. Hydroxyphenstatin was converted to the sodium phosphate prodrug (6e) by a dibenzyl phosphite phosphorylation and subsequent benzyl cleavage (6a --> 6d --> 6e). While hydroxyphenstatin (6a) was a potent inhibitor of tubulin polymerization with activity comparable to that of combretastatin A-1 (3a), the phosphorylated derivative (6e) was inactive.

L7 ANSWER 13 OF 14 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-633578 [54] WPIDS
DOC. NO. CPI: C1999-184978
TITLE: Preparation of **phenstatin** and prodrugs, useful as anti-**cancer** drugs.
DERWENT CLASS: B05
INVENTOR(S): PETTIT, G R; TOKI, B
PATENT ASSIGNEE(S): (UYAR-N) UNIV ARIZONA STATE
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9934788	A1	19990715	(199954)*	EN	37
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CA JP US					
EP 1045689	A1	20001025	(200055)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE					
JP 2002500184	W	20020108	(200206)		41

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9934788	A1	WO 1999-US475	19990109
EP 1045689	A1	EP 1999-902133	19990109
		WO 1999-US475	19990109
JP 2002500184	W	WO 1999-US475	19990109
		JP 2000-527239	19990109

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1045689	A1	Based on	WO 9934788
JP 2002500184	W	Based on	WO 9934788

PRIORITY APPLN. INFO: US 1998-70878P 19980109
AN 1999-633578 [54] WPIDS
AB WO 9934788 A UPAB: 19991221
NOVELTY - Preparation of **phenstatin** uses conventional chemical techniques to improve the yield compared with that obtained from the oxidation of combretastatin A-4.
DETAILED DESCRIPTION - Preparation of **phenstatin** (I) comprises:
(a) oxidizing 3-(t-butyl dimethylsilyl)-oxy-4-methoxybenzaldehyde with potassium permanganate to form the corresponding carboxylic acid;
(b) conversion to the corresponding acid chloride;

(c) coupling the acid chloride with the lithium derivative of 3,4,5-trimethoxybenzene (obtained by treatment with t-butyllithium) to give protected (I); and

(d) deprotection to give (I).

INDEPENDENT CLAIMS are also included for:

(1) prodrugs and derivatives of **phenstatin** of formula (II):

(i) when R = H and R1 = OCH3 then R2 = OPO3Na2, OCOCH3, H or OCH3; and (ii) when R = R2, then R2 = OCH3, CH3, Cl or F and R1 = H; where R1 = R2, then R2 = OCH3 or OCH2O and R = H;

(2) use of **phenstatin** and (II) for inhibiting human **cancer** cell growth;

(3) use of phenastatin prodrug for inhibiting **cancer** cell growth and tubulin polymerization.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Potent inhibitor of tubulin polymerisation and of the binding of colchicine to tubulin.

In tests, (I) gave an IC50 value for inhibition of tubulin polymerization of 1.0 mu M and a value for inhibition of colchicine binding of 86%. In tests on human **cancer** lines (NCI 60 Cell-line human **tumor** screen), (I) and its disodium 3-O-phosphate prodrug gave GI50 values of 6.01 and 7.33 x 10-8 M respectively.

USE - (I) and (II) are potent **antineoplastic** drugs for the treatment of human **cancers**.

ADVANTAGE - This synthetic pathway for (I) provides a more efficient method with yields up to 30% compared with 10% for Jacobsen oxidation of combretastatin-A4.

Dwg.0/0

L7 ANSWER 14 OF 14 MEDLINE on STN DUPLICATE 4

ACCESSION NUMBER: 1998241661 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9572894
TITLE: **Antineoplastic** agents. 379. Synthesis of **phenstatin** phosphate.
AUTHOR: Pettit G R; Toki B; Herald D L; Verdier-Pinard P; Boyd M R; Hamel E; Pettit R K
CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, Arizona 85287-1604, USA.
SOURCE: Journal of medicinal chemistry, (1998 May 7) 41 (10) 1688-95.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980609
Last Updated on STN: 19980609
Entered Medline: 19980528

AB A structure-activity relationship (SAR) study of the South African willow tree (Combretum caffrum) **antineoplastic** constituent combretastatin A-4 (1b) directed at maintaining the (Z)-stilbene relationship of the olefin diphenyl substituents led to synthesis of a potent **cancer** cell growth inhibitor designated **phenstatin** (3b). Initially **phenstatin** silyl ether (3a) was unexpectedly obtained by Jacobsen oxidation of combretastatin A-4 silyl ether (1c --> 3a), and the parent **phenstatin** (3b) was

later synthesized (6a --> 3a --> 3b) in quantity. **Phenstatin** was converted to the sodium phosphate prodrug (3d) by a dibenzyl phosphite phosphorylation and subsequent hydrogenolysis sequence (3b --> 3c --> 3d). **Phenstatin** (3b) inhibited growth of the pathogenic bacterium Neisseriagonorrhoeae and was a potent inhibitor of tubulin polymerization and the binding of colchicine to tubulin comparable to combretastatin A-4 (1b). Interestingly, the prodrugs were found to have reduced activity in these biochemical assays. While no significant tubulin activity was observed with the phosphorylated derivative of combretastatin A-4 (1d), phosphate 3d retained detectable inhibitory effects in both assays.

FILE 'REGISTRY' ENTERED AT 14:23:44 ON 24 SEP 2004

```
=> e "poly(n-isopropylacrylamide)"/cn 5
E1            1      POLY(N-ISOPROPYL-N'-PHENYL-P-PHENYLENEDIAMINE)/CN
E2            1      POLY(N-ISOPROPYL-N'-PHENYLACRYLAMIDINE)/CN
E3            1 --> POLY(N-ISOPROPYLACRYLAMIDE)/CN
E4            1      POLY(N-ISOPROPYLACRYLAMIDE-CO-METHACRYLIC ACID)/CN
E5            1      POLY(N-ISOPROPYLIMINOALANE)/CN

=> s e3
L8            1 "POLY(N-ISOPROPYLACRYLAMIDE)"/CN
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(FILE 'CAPLUS' ENTERED AT 14:24:23 ON 24 SEP 2004)

```
L1            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  PHENSTATIN/CN
L2           13 SEA FILE=CAPLUS ABB=ON  PLU=ON  L1 OR PHENSTATIN
L8            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "POLY(N-ISOPROPYLACRYLAMIDE)"
                /CN
L9         2726 SEA FILE=CAPLUS ABB=ON  PLU=ON  L8 OR POLY(W)(N(W)(ISOPROPYLACR
                YLAMIDE OR (ISO OR I)(W)(PROPYLACRYLAMIDE OR (PROPYL OR
                PR)(W)(ACRYLAMIDE OR ACRYL AMIDE) OR PROPYLACRYL AMIDE) OR
                ISOPROPYL(W)(ACRYLAMIDE OR ACRYL AMIDE))) OR PNIPA
L10           0 SEA FILE=CAPLUS ABB=ON  PLU=ON  L2 AND L9


L8            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "POLY(N-ISOPROPYLACRYLAMIDE)"
                /CN
L9         2726 SEA FILE=CAPLUS ABB=ON  PLU=ON  L8 OR POLY(W)(N(W)(ISOPROPYLACR
                YLAMIDE OR (ISO OR I)(W)(PROPYLACRYLAMIDE OR (PROPYL OR
                PR)(W)(ACRYLAMIDE OR ACRYL AMIDE) OR PROPYLACRYL AMIDE) OR
                ISOPROPYL(W)(ACRYLAMIDE OR ACRYL AMIDE))) OR PNIPA
L11          34 SEA FILE=CAPLUS ABB=ON  PLU=ON  L9 AND (?NEOPLAS? OR ?CANCER?
                OR ?CARCIN? OR ?TUMOUR? OR ?TUMOR? OR ?SARCOMA? OR ?MELANOMA?)
L12           4 SEA FILE=CAPLUS ABB=ON  PLU=ON  L11 AND (BREAST OR MAMMAR? OR
                PROSTAT## OR LUNG OR BOWEL OR GASTRIC OR COLON OR COLONIC OR
                COLORECTAL OR STOMACH)


L13           4 L12 NOT L3
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L13  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2004 ACS on STN
ED   Entered STN:  14 May 2004
ACCESSION NUMBER:        2004:391539  CAPLUS
DOCUMENT NUMBER:         140:386061
TITLE:                   Screening of compounds with specific site affinity,
                         probes for the process, and use of oligosaccharides
                         for drug delivery, diagnostic agents, and
```

pharmaceuticals
INVENTOR(S): Murakami, Tatsuya; Suzawa, Toshiyuki; Yamazaki, Motoo; Sato, Mitsuo; Endo, Tetsuo; Koizumi, Satoshi; Imada, Teruyoshi
PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 25 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2004138397	A2	20040513	JP 2002-300742	20021015
PRIORITY APPLN. INFO.:			JP 2002-300742	20021015

AB Probes of (S1L1)mB1F1n (S1 = residue of test compds.; L1 = biocompatible polymer residue; F1 = imaging agent residue; B1 = linker; m = 1-60; n = 0-10), useful for screening of drugs and diagnostic agents, are administered to exptl. animals, then the whole animals, their organs, tissues, or cells are subjected to image anal. after a certain period of time to determine the probes and identify organs, tissues, or cells where the probes are accumulated. Compds. containing physiol. active substance residues and residues of Galβ1-4GlcNAcβ1-3Galβ1-4Glc (LNnT) or its motif-containing oligosaccharides are delivered specifically to pancreas, thymus, testis, and/or **prostate.** Thus, (LNnT-L)p-BSA-F (L = polyethylene glycol residue; BSA = bovine serum albumin; F = fluorescein isothiocyanate residue) was i.v. administered to mice. After 24 h, fluorescent images of the organs showed specific accumulation of the compound to pancreas and **prostate.**

IT **25189-55-3, Poly(N-isopropylacrylamide)**
RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(linker; screening and organ-specific delivery of drugs and diagnostic agents)

L13 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 06 Jun 2003
ACCESSION NUMBER: 2003:434581 CAPLUS
DOCUMENT NUMBER: 139:17916
TITLE: Synthesis and uses of pentapeptides for the treatment of PDGF receptor-mediated cell proliferation disorders
INVENTOR(S): Dean, Cheryl; Heidaran, Mohammad; Spargo, Cathy A.
PATENT ASSIGNEE(S): Becton, Dickinson and Company, USA; Haaland, Perry D.
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2003045973 A2 20030605 WO 2002-US31165 20020930
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2003175745 A1 20030918 US 2002-259816 20020930
PRIORITY APPLN. INFO.: US 2001-333476P P 20011128

AB Peptides and peptide compns. are identified which inhibit the adhesion and growth of abnormal cells. In one embodiment, the peptides are useful for inhibiting the growth of cells dependent on autocrine activation of the PDGF receptor. Such peptides may be used in the treatment of cell proliferative disorders including **cancer**, fibrotic disorders, myeloproliferative diseases and blood vessel proliferative (angiogenic) disorders characterized by inappropriate PDGF receptor activity. A biomedical device is further disclosed which has associated with it a peptide or peptide composition according to the present invention.

IT **25189-55-3**, Polyisopropylacrylamide
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(synthesis and uses of polymer-bounded pentapeptides for treatment of PDGF receptor-mediated cell proliferation disorders)

L13 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 24 Dec 2000
ACCESSION NUMBER: 2000:903401 CAPLUS
DOCUMENT NUMBER: 135:55345
TITLE: Chemosensitivity test of human **cancer** cell lines in three-dimensional culture using thermoreversible gelation polymer
AUTHOR(S): Yoshikawa, Takeshi; Tsukikawa, Satoshi
CORPORATE SOURCE: First Department of Surgery, St. Marianna University School of Medicine, Kawasaki, 216-8511, Japan
SOURCE: Sei Marianna Ika Daigaku Zasshi (2000), 28(4), 477-486
CODEN: SMIZDS; ISSN: 0387-2289
PUBLISHER: Sei-Marianna Ika Daigaku Igakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB When the sensitivity to **anticancer** drugs is evaluated using the conventional monolayer culture method, the effects of contamination such as fibroblasts or cellular damage often generate results in different actual clin. outcomes. Thermoreversible gelation polymer (TGP) is a copolymer of **poly** (**N-isopropylacrylamide**)-gelation which shows a reversible change from gelation to solution at the transition temperature of 22°. In TGP containing culture medium, **cancerous** cells proliferate in a three-dimensional manner to form spheroids. This technique has enabled us to evaluate sensitivity to **anticancer** drugs under similar conditions in vivo. The present author evaluated the sensitivity of seven **cancerous** cell strains

to **anticancer** drugs using both the new three-dimensional culture method (TGP method) and the conventional monolayer culture method in order to make a comparative study of these two techniques. Each **cancerous** cell strain was cultivated using the TGP method and the monolayer culture method for 72 h. An **anticancer** drug was then added to the culture media. The **cancerous** cell strains were exposed to the **anticancer** drug either for 24 h or for 72 h. The sensitivity to the **anticancer** drug was compared between these two treatment groups. The forms and rates of proliferation of **cancerous** cell strains and normal human **lung** fibroblasts (NHLF) were also observed Unlike the monolayer culture group, the TGP group showed a decrease in the survival rate in a concentration-dependent manner. In the TGP group, the half inhibiting concentration (IC50) was easily calculated, and, the value was low. Spheroid formation was observed in all the **cancerous** strains cultivated in TGP containing culture medium, while NHLF showed no such cellular proliferation. Accordingly, the TGP method was regarded as being a useful technique for long-term culture maintaining similar conditions in vivo.

L13 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 28 Apr 1995
ACCESSION NUMBER: 1995:513772 CAPLUS
DOCUMENT NUMBER: 122:260567
TITLE: Substrate support coated with collagen and thermal-sensitive polymer and cell growth factors for selectively growing **tumor** cells
INVENTOR(S): Takano, Toshikazu; Hizuka, Masahiro
PATENT ASSIGNEE(S): Nitta Gelatin Kk, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 14 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 07031470	A2	19950203	JP 1993-180504	19930721
PRIORITY APPLN. INFO.:			JP 1993-180504	19930721

AB Disclosed is a method for inhibiting the extension and growth of normal cells and selectively proliferating **tumor** cells. The method comprises culturing a mixture of normal and **cancer** cells on a substrate support coated with collagen, cell growth factors, and thermal-sensitive polymer. In example, plastic dish coated with type I collagen and **poly-N-isopropylacrylamide** for selectively proliferating **colon** or **lung cancer** cells.

IT **25189-55-3, Poly-N-isopropylacrylamide**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(method using substrate support coated with polymer and cell growth factors for selectively growing **tumor** cells)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS,

JAPIO, CANCERLIT' ENTERED AT 14:28:32 ON 24 SEP 2004)

L14 1 S L10
L15 17 S L12

L8 1 SEA FILE=REGISTRY ABB=ON PLU=ON "POLY(N-ISOPROPYLACRYLAMIDE)"/CN
L9 2726 SEA FILE=CAPLUS ABB=ON PLU=ON L8 OR POLY(W)(N(W)(ISOPROPYLACRYLAMIDE OR (ISO OR I)(W)(PROPYLACRYLAMIDE OR (PROPYL OR PR)(W)(ACRYLAMIDE OR ACRYL AMIDE) OR PROPYLACRYL AMIDE) OR ISOPROPYL(W)(ACRYLAMIDE OR ACRYL AMIDE))) OR PNIPA
L16 39 SEA L9 AND (ANTINEOPLAS? OR ANTICANCER? OR ANTICARCIN? OR ANTITUMOUR? OR ANTITUMOR? OR ANTISARCOMA? OR ANTIMELANOMA?)
L17 10 SEA L16 AND (BREAST OR MAMMAR? OR PROSTAT## OR LUNG OR BOWEL OR GASTRIC OR COLON OR COLONIC OR COLORECTAL OR STOMACH)

L18 16 (L14 OR L15 OR L17) NOT L6

PROCESSING COMPLETED FOR L18
L19 11 DUP REM L18 (5 DUPLICATES REMOVED)

L19 ANSWER 1 OF 11 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-444115 [42] WPIDS
DOC. NO. NON-CPI: N2004-351185
DOC. NO. CPI: C2004-166661
TITLE: Screening compounds accumulated on specific organs of non-human animals, by administering a probe, assaying the probe from extracted organs and identifying organs in which test compound accumulates.
DERWENT CLASS: A96 B04 D16 S03
PATENT ASSIGNEE(S): (KYOW) KYOWA HAKKO KOGYO KK
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
JP 2004138397	A	20040513	(200442)*		25

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 2004138397	A	JP 2002-300742	20021015

PRIORITY APPLN. INFO: JP 2002-300742 20021015
AN 2004-444115 [42] WPIDS
AB JP2004138397 A UPAB: 20040702
NOVELTY - Screening (M1) compounds accumulated on the specific region of a non-human animal, involves administering a probe having a specific formula to animals, assaying the probe from the organ extracted from the animal or by image measurement of cell, after fixed time, and identifying the organ, tissue or cell in which the test compound accumulates, is new.
DETAILED DESCRIPTION - Screening (M1) compounds accumulated on the specific region of an animal, involves administering probe having formula (I), to animals other than human assaying the probe from the extracted

organ or by image measurement of cell, after fixed time, and identifying the organ, tissue or cell in which the test compound accumulates.

(S1-L1)m-B1-(F1)n (I)

L1 = position specific and biocompatible polymeric residue that can chemically combine S1 and B1;

F1 = image-formation reagent residue;

B1 = combines 1-60 L1 and 1-10 F1 by B1 or linker binding with 1-60 L1;

m = 1-60; and

n = 0-10.

INDEPENDENT CLAIMS are included for:

(1) a probe (I) for an integrated region detection of test compound in living organism, comprising formula as represented in (M1);

(2) an organ delivery compound (II) that can transport bioactive substance to specific organ chosen from pancreas, thymuses, testis and **prostate** gland, comprising bioactive substance residue of oligo sugar derivative moiety that has LNnT motif, where LNnT represents Gal-beta 1-4GlcNAc- beta 1-3Gal- beta 1-4Glc;

(3) a therapeutic or preventive agent (III) for hyperactivity of cell or disease that accompanies dysfunction of cell of organ e.g., pancreas, **prostate** gland or thymuses;

(4) use of an oligo sugar derivative moiety (IV) that has LNnT motif as mentioned in (II), for manufacture of organ delivery compound which transports the bioactive substance to organ chosen from pancreas, thymuses, testis and **prostate** gland; and

(5) an oligo sugar derivative moiety expressed by NeuAc- alpha 2-6Gal- beta 1-4GlcNAc- beta 1-3Gal- beta 1-4Glc, or o-acetyl (Gal- beta 1-4GlcNAc- beta 1-3Gal- beta 1-4Glc).

ACTIVITY - Cytostatic; Antiinflammatory; Antidiabetic; Immunosuppressive; Antiasthmatic; Antiallergic; Anti-HIV; Antiarthritic; Antirheumatic; Nephrotropic.

No biological data given.

MECHANISM OF ACTION - None given.

USE - (M1) is useful for screening compounds that accumulate on specific organs of an animal other than human. (II) is useful for diagnosing hyperactivity of a cell and disease accompanying dysfunction of cell present in pancreas, **prostate** gland or thymuses. The disease accompanying the dysfunction of the cell comprises pancreatic **carcinoma**, acute pancreatitis, chronic pancreatitis, diabetes, **prostate cancer**, autoimmune disease, allergy, atopy, asthma, hay fever, airways anaphylaxis, HIV infection, rheumatoid arthritis, transplant-pair-host disease, insulin-dependent diabetes mellitus or glomerulonephritis. (III) is useful for preventing the above diseases. (IV) is useful for manufacturing organ delivery compound that can transport bioactive substance to organ chosen from pancreas, thymuses, testis and **prostate** gland (claimed).

ADVANTAGE - (M1) enables to screen compounds that accumulate on specific organs of an animal other than human.

Dwg.0/1

L19 ANSWER 2 OF 11 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:344329 BIOSIS

DOCUMENT NUMBER: PREV200400340917

TITLE: Preparation and characterization of water-soluble pH-sensitive nanocarriers for drug delivery.

AUTHOR(S): Dufresne, M.-H.; Le Garrec, D.; Sant, V.; Leroux, J.-C. [Reprint Author]; Ranger, M.
CORPORATE SOURCE: Fac PharmCanada Res Chair Drug Delivery, Univ Montreal, CP 6128,Succ Ctr Ville, Montreal, PQ, H3C 3J7, Canada jean-christophe.leroux@umontreal.ca
SOURCE: International Journal of Pharmaceutics (Kidlington), (June 11 2004) Vol. 277, No. 1-2, pp. 81-90. print. ISSN: 0378-5173 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Aug 2004
Last Updated on STN: 11 Aug 2004

AB pH-sensitive drug delivery systems can be engineered to release their contents or change their physicochemical properties in response to variations in the acidity of the surroundings. The present work describes the preparation and characterization of novel polymeric micelles (PM) composed of amphiphilic pH-responsive **poly(N-isopropylacrylamide)** (PNIPAM) or poly(alkyl(meth)acrylate) derivatives. On one hand, acidification of the PNIPAM copolymers induces a coil-to-globule transition that can be exploited to destabilize the intracellular vesicle membranes. In this work, PNIPAM-based PM were loaded with either doxorubicin or aluminium chloride phthalocyanine and their cytotoxicity was assessed in murine **tumoral** models. On the other hand, poly(alkyl(meth)acrylate) copolymers can be designed to interact with either hydrophobic drugs or polyions and release their cargo upon an increase in pH.

L19 ANSWER 3 OF 11 JICST-EPlus COPYRIGHT 2004 JST on STN
ACCESSION NUMBER: 1030789405 JICST-EPlus
TITLE: Temperature-dependent Regulation of Antisense Activity Using a DNA/**poly(N-isopropylacrylamide)** Conjugate
AUTHOR: MURATA M; KAKU W; ANADA T; SATO Y; MAEDA M; KATAYAMA Y
CORPORATE SOURCE: Kyushu Univ., Fukuoka
SOURCE: Chem Lett, (2003) vol. 32, no. 11, pp. 986-987. Journal Code: S0742A (Fig. 2, Ref. 14)
CODEN: CMLTAG; ISSN: 0366-7022
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Short Communication
LANGUAGE: English
STATUS: New

AB We prepared a novel antisense reagent comprising of oligodeoxynucleotides (ODNs) and a thermo-responsive polymer, **poly(N-isopropylacrylamide)** (PNIPAAm). The conjugate demonstrated stimuli-responsive regulation of gene expression via conformational change of the polymer chain. (author abst.)

L19 ANSWER 4 OF 11 EMBASE on STN
ACCESSION NUMBER: 2003346693 EMBASE
TITLE: New possibilities of application of multifunctional polymers and polymer conjugates.
AUTHOR: Pluta J.; Karolewicz B.
CORPORATE SOURCE: J. Pluta, Department of Dispensing Pharmacy, Wroclaw Medical University, 38 Szewska Str., 50-139 Wroclaw, Poland

SOURCE: Acta Poloniae Pharmaceutica - Drug Research, (2003) 60/3 (211-214).
Refs: 27
ISSN: 0001-6837 CODEN: APPHAX
COUNTRY: Poland
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Present review provides examples of new applications of multifunctional polymers and polymer conjugates, i. e. polymer-active substance conjugates, polymer-protein conjugates, in pharmacy and medicine.

L19 ANSWER 5 OF 11 EMBASE
on STN DUPLICATE 1
ACCESSION NUMBER: 2002298242 EMBASE
TITLE: Optimizing pH-responsive polymeric micelles for drug delivery in a **cancer** photodynamic therapy model.
AUTHOR: Le Garrec D.; Taillefer J.; Van Lier J.E.; Lenaerts V.; Leroux J.-C.
CORPORATE SOURCE: J.-C. Leroux, Canada Res. Chair in Drug Delivery, Faculty of Pharmacy, University of Montreal, C.P. 6128 Succ. Centre-ville, Montreal, Que. H3C 3J7, Canada. jean-christophe-leroux@umontreal.ca
SOURCE: Journal of Drug Targeting, (2002) 10/5 (429-437).
Refs: 46
ISSN: 1061-186X CODEN: JDTAEH
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
016 Cancer
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Different pH-sensitive, randomly- and terminally-alkylated N-isopropylacrylamide (NIPAM) copolymers were synthesized and used to prepare pH-responsive polymeric micelles (PM). These copolymers were modified from previously-studied copolymers by incorporating an additional hydrophilic monomer, N-vinyl-2-pyrrolidone (VP) to decrease uptake by the mononuclear phagocyte system (MPS) and improve localization in **tumors**. VP lowered the phase transition pH of the copolymers but did not affect the onset of micellization. The in vitro cytotoxicity of the copolymers was evaluated on EMT-6 mouse **mammary tumor** cells in comparison to Cremophor EL (CRM). The **anticancer** photosensitizer aluminum chloride phthalocyanine (AlClPc) was loaded into the PM with a standard dialysis procedure. Biodistribution and in vivo photodynamic activity were then evaluated in Balb/c mice bearing intradermal EMT-6 **tumors**. All NIPAM copolymers demonstrated substantially lower cell cytotoxicity than the

control surfactant CRM. In vivo, similar AlClPc **tumor** uptake was observed for the PM and CRM formulations. However, the PM appeared to exhibit greater activity in vivo than CRM formulation at an AlClPc subtherapeutic dose. Therefore, NIPAM-based copolymers containing VP units represent promising alternatives for the formulation of poorly water-soluble phthalocyanines.

L19 ANSWER 6 OF 11 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 2

ACCESSION NUMBER: 2001069230 EMBASE
TITLE: In-vitro and in-vivo evaluation of pH-responsive polymeric micelles in a photodynamic **cancer** therapy model.
AUTHOR: Taillefer J.; Brasseur N.; Van Lier J.E.; Lenaerts V.; Le Garrec D.; Leroux J.-C.
CORPORATE SOURCE: J.-C. Leroux, Faculty of Pharmacy, University of Montreal, C. P. 6128 Succ. Centre-ville, Montreal, Que. H3C 3J7, Canada. leroujea@pharm.umontreal.ca
SOURCE: Journal of Pharmacy and Pharmacology, (2001) 53/2 (155-166).
Refs: 44
ISSN: 0022-3573 CODEN: JPPMAB
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
019 Rehabilitation and Physical Medicine
030 Pharmacology
039 Pharmacy
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB pH-sensitive polymeric micelles of randomly and terminally alkylated N-isopropylacrylamide copolymers were prepared and characterized. Aluminium chloride phthalocyanine (AICIPc), a second generation sensitizer for the photodynamic therapy of **cancer**, was incorporated in the micelles by dialysis. Their photodynamic activities were evaluated in-vitro against EMT-6 mouse **mammary tumour** cells and in-vivo against EMT-6 **tumours** implanted intradermally on each hind thigh of Balb/c mice. pH-sensitive polymeric micelles were found to exhibit greater cytotoxicity in-vitro than control Cremophor EL formulations. In the presence of chloroquine, a weak base that raises the internal pH of acidic organelles, in-vitro experiments demonstrated the importance of endosomal/lysosomal acidity for the pH-sensitive polymeric micelles to be fully effective. Biodistribution was assessed by fluorescence of tissue extracts after intravenous injection of 2 μmol kg(-1) AICIPc. The results revealed accumulation of AICIPc polymeric micelles in the liver, spleen and **lungs**, with a lower **tumour** uptake than AICIPc Cremophor EL formulations. However, polymeric micelles exhibited similar activity in-vivo to the control Cremophor EL formulations, demonstrating the higher potency of AICIPc polymeric micelles when localized in **tumour** tissue. It was concluded that polymeric micelles represent a good alternative to Cremophor EL preparations for the vectorization of hydrophobic drugs.

L19 ANSWER 7 OF 11 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2001:527608 SCISEARCH

THE GENUINE ARTICLE: 445MZ
TITLE: N-isopropylacrylamide copolymers for the preparation of pH-sensitive liposomes and polymeric micelles
AUTHOR: Leroux J C (Reprint); Roux E; Le Garrec D; Hong K L; Drummond D C
CORPORATE SOURCE: Univ Montreal, Fac Pharm, CP 6128 Succ Ctr Ville, Montreal, PQ H3C 3J7, Canada (Reprint); Univ Montreal, Fac Pharm, Montreal, PQ H3C 3J7, Canada; Calif Pacific Med Ctr, Res Inst, San Francisco, CA 94115 USA
COUNTRY OF AUTHOR: Canada; USA
SOURCE: JOURNAL OF CONTROLLED RELEASE, (14 MAY 2001) Vol. 72, No. 1-3, pp. 71-84.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0168-3659.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 87

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Hydrophobically-modified copolymers of N-isopropylacrylamide bearing a pH-sensitive moiety were investigated for the preparation of pH-responsive liposomes and polymeric micelles. The copolymers having the hydrophobic anchor randomly distributed within the polymeric chain were found to more efficiently destabilize egg phosphatidylcholine (EPC)/cholesterol liposomes than the alkyl terminated polymers. Release of both a highly-water soluble fluorescent contents marker, pyranine, and an amphipathic cytotoxic anti-**cancer** drug, doxorubicin, from copolymer-modified liposomes was shown to be dependent on pH, the concentration of copolymer, the presence of other polymers such as polyethylene glycol, and the method of preparation. Both polymers were able to partially stabilize EPC liposomes in human serum. These polymers were found to self-assemble to form micelles. The critical association concentration was low (9-34 mg/l) and influenced by the position of the alkyl chains. In phosphate buffered saline, the micelles had a bimodal size distribution with the predominant population having a mean diameter of 35 nm. The polymeric micelles were studied as a delivery system for the photosensitizer aluminum chloride phthalocyanine, (AlClPc), currently evaluated in photodynamic therapy. pH-Responsive polymeric micelles loaded with AlClPc were found to exhibit increased cytotoxicity against EMT-6 mouse **mammary** cells in vitro than the control Cremophor EL formulation.

L19 ANSWER 8 OF 11 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2001099601 EMBASE
TITLE: Design of nanoparticles composed of graft copolymers for oral peptide delivery.
AUTHOR: Sakuma S.; Hayashi M.; Akashi M.
CORPORATE SOURCE: S. Sakuma, Pharmaceut. Formulation Res. Lab., Daiichi Pharmaceutical Co. Ltd., 1-Chome, Edogawa-ku, Tokyo 134-8630, Japan. sakumv8j@daiichipharm.co.jp
SOURCE: Advanced Drug Delivery Reviews, (23 Mar 2001) 47/1 (21-37). Refs: 134
ISSN: 0169-409X CODEN: ADDREP
PUBLISHER IDENT.: S 0169-409X(00)00119-8
COUNTRY: Netherlands

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The development of a dosage form that improves the absorption of peptide and protein drugs via the gastrointestinal tract is one of the greatest challenges in the pharmaceutical field. Many researchers have taken up the challenge, using approaches including mucoadhesive drug delivery, **colon** delivery, particulate drug delivery such as nanoparticles, microcapsules, liposomes, emulsions, micelles, and so on. The objective of this article is to provide the reader with outlines of novel nanoparticle technologies for oral peptide delivery based on polymer chemistry. The physicochemical properties of nanoparticles and their behavior on exposure to physiological media are greatly dominated by their chemical structures and surface characteristics. We will especially focus on the design of nanoparticles composed of novel graft copolymers having a hydrophobic backbone and hydrophilic branches as drug carriers. .COPYRGT. 2001 Elsevier Science B.V.

L19 ANSWER 9 OF 11 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2000130386 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10664538
TITLE: Preparation and characterization of pH-responsive polymeric micelles for the delivery of photosensitizing **anticancer** drugs.
AUTHOR: Taillefer J; Jones M C; Brasseur N; van Lier J E; Leroux J C
CORPORATE SOURCE: Faculty of Pharmacy, University of Montreal, Montreal, Quebec, Canada H3C 3J7.
SOURCE: Journal of pharmaceutical sciences, (2000 Jan) 89 (1) 52-62.
Journal code: 2985195R. ISSN: 0022-3549.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000407

AB pH-responsive polymeric micelles (PM) consisting of random copolymers of N-isopropylacrylamide (NIPA), methacrylic acid (MAA), and octadecyl acrylate (ODA) were prepared and characterized. The critical aggregation concentration, as determined by a fluorescence probe technique, was approximately 10 mg/L in water and phosphate-buffered saline. Phase transition pH was estimated at 5.7. The decrease in pH was accompanied by the destruction of hydrophobic clusters. Micelle size was dependent on temperature and the nature of the aqueous medium. The micelles were successfully loaded with a substantial amount of a photoactive **anticancer** drug, namely, aluminum chloride phthalocyanine (AlClPc). pH-responsive PM loaded with AlClPc were found to exhibit higher cytotoxicity against EMT-6 mouse **mammary** cells in vitro than control Cremophor EL formulation. These results show the potential of

poly(NIPA-co-MAA-co-ODA) for in vivo administration of water-insoluble, photosensitizing **anticancer** drugs.
Copyright 2000 Wiley-Liss, Inc. and the American Pharmaceutical Association J Pharm Sci 89: 52-62, 2000

L19 ANSWER 10 OF 11 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1995-109527 [15] WPIDS
DOC. NO. CPI: C1995-049650
TITLE: Inhibiting growth of **cancer** cells without damaging normal cells - includes culturing **cancer** cells containing normal cells on surface of culture medium, mainly of synthetic high polymer and cell growth factor.
DERWENT CLASS: B04 D16
PATENT ASSIGNEE(S): (NITT-N) NITTA GELATIN KK
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
JP 07031470	A	19950203	(199515)*		14

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 07031470	A	JP 1993-180504	19930721

PRIORITY APPLN. INFO: JP 1993-180504 19930721
AN 1995-109527 [15] WPIDS
AB JP 07031470 A UPAB: 19950425
Cancer cells containing normal cells are cultured on the surface of a culture medium consisting substantially of a synthetic high polymer and a cell growth factor and the **cancer** cells are selectively grown.
The culture medium is prepared by applying a coating solution preparation by mixing a synthetic high polymer and a cell growth factor with water on the culture substrate.
ADVANTAGE - The method stops or inhibits growth of normal cells and requires no chemical for killing normal cells.
In an example, same amts. of 0.3% aqueous collagen solution and 1/0% aqueous **poly-N-isopropylacrylamide** (PNIPPAm) solution were mixed together and stirred at 4 deg.C fo 1 day to prepare a coating solution 0.5 ml of the solution was poured on a plastic dish at 28 deg.C and dried overnight. It was heated to 37 deg.C and 1 ml of a cell suspension containing 4 multiplied by ten to part of five cells/ml of **colon cancer** cells (DLD-1) in a Dulbecco-modified Eagle medium containing 10% FBS was inoculated to it and cultured at 37 deg.C for 4 days. The condition on the dish surface was observed by a phase-contrast microscope.
Dwg.0/23

L19 ANSWER 11 OF 11 JICST-EPlus COPYRIGHT 2004 JST on STN
ACCESSION NUMBER: 940024884 JICST-EPlus
TITLE: Morphological Studies of Multicellular Spheroids of Cholangiocarcinoma Cell Line and Human **Cancer**

Cells from Patient Specimens Cocultured with Fibroblasts on Thermo-responsive Polymer.

AUTHOR: OGATA HARUKI
CORPORATE SOURCE: St. Marianna Univ. School of Medicine
SOURCE: Sei Marianna Ika Daigaku Zasshi (St. Marianna Medical Journal), (1993) vol. 21, no. 4, pp. 703-712. Journal Code: Z0605A (Fig. 10, Tbl. 2, Ref. 18)
ISSN: 0387-2289
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New

AB As a substratum for producing multicellular spheroids of **cancer** cell line and human **cancer** cells from patient specimens cocultured with human dermal fibroblasts, a thermo-responsive polymer, **poly-N-isopropylacrylamide** (PNIPAAm) conjugated with collagen was used. Pre-warmed fibroblast suspension was spread on collagen conjugated PNIPAAm coating dish, and cultured for 3 days. Thereafter, cholangiocarcinoma cell line (MEC) or human **cancer** cells from patient specimens were scattered on this fibroblastic sheet. By the decrease in ambient temperature to 25.DEG.C., the sheet of fibroblasts-adhered MEC cells or human **cancer** cells started to detach itself from the dish and changed into a multicellular spheroid. Twenty-six cases of multicellular spheroids of fibroblasts and human **cancer** cells from patient specimens were from 9 **breast**, 1 thyroid, 8 **gastric**, and 8 **colon cancers**. In 19 cases, human **cancer** cells grew into multicellular spheroids, but 7 cases from 2 **breast**, 1 **gastric**, and 4 **colon cancers** did not. Histological examination of a 14-day-old spheroid containing MEC showed differentiated adenocarcinoma, which closely resembled the original **tumor**. However, that of a 14-day-old spheroid containing human **cancer** cells did not show in-vivo structure. (author abst.)

FILE 'CAPLUS' ENTERED AT 14:32:33 ON 24 SEP 2004
L20 2 S PNIPPAAM
L21 2 S L20 NOT (L3 OR L13)

L21 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 26 Mar 2002
ACCESSION NUMBER: 2002:228122 CAPLUS
DOCUMENT NUMBER: 136:259589
TITLE: Single stranded DNA-poly(N-isopropylacrylamide) conjugate for reversible antisense gene expression regulation
INVENTOR(S): Maeda, Sumio; Katayama, Yoshiki; Murata, Shoji; Kano, Takeshi
PATENT ASSIGNEE(S): Foundation for Scientific Technology Promotion, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

JP 2002085065	A2	20020326	JP 2000-272151	20000907
PRIORITY APPLN. INFO.:			JP 2000-272151	20000907

AB A method for reversible antisense regulation of gene expression using a DNA conjugate comprising single-stranded DNA and a hydrophobic substance is disclosed. The conjugate between single-stranded DNA and the temperature-responsive polymer poly(N-isopropylacryl-amide) (**PNIPPAAm**) was synthesized, and was used to regulate the expression of GFP reporter gene. Methacryloyloxy succinimide was reacted with 3'-C7 amino oligodeoxynucleotide (ODN) to obtain vinyl ODN, which was reacted with N-isopropylacrylamide in a radical chain reaction using TEMED as initiator.

L21 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 29 Oct 2001
ACCESSION NUMBER: 2001:783614 CAPLUS
DOCUMENT NUMBER: 136:115014
TITLE: Formation of DNA-carrying colloidal particle from poly(N-isopropylacrylamide)-graft-DNA copolymer and its assembly through hybridization
AUTHOR(S): Mori, Takeshi; Maeda, Mizuo
CORPORATE SOURCE: Department of Applied Chemistry, Graduate School of Engineering, Kyushu University, Fukuoka, 812-8581, Japan
SOURCE: Polymer Journal (Tokyo, Japan) (2001), 33(10), 830-833
CODEN: POLJB8; ISSN: 0032-3896
PUBLISHER: Society of Polymer Science, Japan
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A one-step preparation of DNA-carrying colloidal nanoparticle through the self-organization of copolymer, composed of poly(N-isopropylacrylamide) (**PNIPPAAm**) main chain and DNA graft chain, is described. The narrowly distributed DNA-carrying colloidal particles are easily prepared from **PNIPPAAm**-graft-DNA by heating. The particle surface DNA recognizes the complementary crosslinking DNA so that the particle assembly is formed. This particle would be applicable for the turbidimetric DNA detection.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 14:33:25 ON 24 SEP 2004)

L22 2 S L20
L23 2 S L22 NOT (L6 OR L18)
L24 2 DUP REM L23 (0 DUPLICATES REMOVED)

L24 ANSWER 1 OF 2 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003481960 EMBASE
TITLE: Thermo-responsive **PNiPPAAm**-g-PEG films of controlled cell detachment.
AUTHOR: Schmalijohann D.; Oswald J.; Jorgensen B.; Nitschke M.; Beyerlein D.; Werner C.
CORPORATE SOURCE: D. Schmaljohann, Institute of Polymer Res. Dresden, Max Bergmann Ctr. of Biomat. Dresden, Hohe Str. 6, 01069 Dresden, Germany. schmalijohann@ipfdd.de

Searcher : Shears 571-272-2528

SOURCE: Biomacromolecules, (2003) 4/6 (1733-1739).
Refs: 34
ISSN: 1525-7797 CODEN: BOMAF6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A series of graft copolymers consisting of either poly(N-isopropylacrylamide) (PNiPAAm) or poly(N,N-diethylacrylamide) (PDEAAm) as a thermo-responsive component in the polymer backbone and poly-(ethyleneglycol) (PEG) were immobilized as thin films and cross-linked on a fluoropolymer substrate using low-pressure argon plasma treatment. The surface-immobilized hydrogels exhibit a transition from partially collapsed to completely swollen, which is in the range of 32-35 °C and corresponds to the lower critical solution temperature of the soluble polymers. The hydrogels were used as cell carriers in culture experiments with L929 mouse fibroblast cells to probe for cell adhesion, proliferation, and temperature-dependent detachment of cell layers. The fibroblast cells adhere, spread, and proliferate on the hydrogel layers at 37 °C and become completely detached after reducing the temperature by 3 K. The cell release characteristics were further correlated to the swelling and collapsing behavior of the hydrogel films and the polymer solutions as measured in PBS solution and RPMI cell cultivation medium. It could be shown that, long before the swelling has completed upon temperature reduction, the cells detach. This can be attributed to the large content of PEG present in the hydrogel, which weaken the cell adhesion strength to the hydrogel layers.

L24 ANSWER 2 OF 2 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 97:406850 SCISEARCH
THE GENUINE ARTICLE: XA252
TITLE: Fast responsive poly(N-isopropylacrylamide) hydrogels prepared by gamma-ray irradiation
AUTHOR: Kishi R (Reprint); Hirasa O; Ichijo H
CORPORATE SOURCE: NATL INST MAT & CHEM RES, DEPT POLYMER ENGN, TSUKUBA, IBARAKI 305, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: POLYMER GELS AND NETWORKS, (APR 1997) Vol. 5, No. 2, pp. 145-151.
Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, OXON, ENGLAND OX5 1GB.
ISSN: 0966-7822.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: ENGI
LANGUAGE: English
REFERENCE COUNT: 14

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB gamma-ray irradiation of N-isopropylacrylnmide (NIPAAm) monomer solution resulted in the formation of the opaque poly(N-isopropylacrylamide) (**PNIPPAAm**) gel having a microporous structure. The thermo-responsive properties of the microporous gel were the same as that of a homogeneous gel prepared by conventional methods.

The gel swelled below and shrunk above the lower critical solution temperature (LCST) (33 degrees C). The rapid and reversible volume change was observed by changing temperature. (C) 1997 Elsevier Science Limited.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 14:48:40 ON 24 SEP 2004)

L25 0 S L2 AND ANTIADENOCARCINOM?

L26 0 S L9 AND ANTIADENOCARCINOM?

FILE 'REGISTRY' ENTERED AT 14:34:00 ON 24 SEP 2004

=> e phenstatin acrylate/cn 5

E1	1		PHENSTATIN/CN
E2	1		PHENSTATIN ACETATE/CN
E3	0	-->	PHENSTATIN ACRYLATE/CN
E4	1		PHENSTATIN DIBENZYL PHOSPHATE/CN
E5	1		PHENSTATIN DISODIUM PHOSPHATE/CN

=> fil hom

FILE 'HOME' ENTERED AT 14:34:27 ON 24 SEP 2004